AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Bicalutamide
Study Code	D6874C00008 (D6876L00011)
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A pharmacoepidemilogy study on the association between bicalutamide treated prostate cancer and risk of coronary heart disease (CHD) and heart failure (HF) in the UK General Practice Research Database (GPRD)

Study dates: Study start date: December 2007
Study completion date: June 2009

Phase of development: Therapeutic use

This study was performed in compliance with Good Pharmacoepidemiology Practice, including the archiving of essential documents.

Study centre(s)

UK

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

1. To compare the risk of serious coronary heart disease (acute myocardial infarction or death from coronary heart disease) and heart failure in prostate cancer patients compared with that in the general population.

2. To compare the risk of serious coronary heart disease (acute myocardial infarction or death from coronary heart disease) and heart failure in prostate cancer patients treated with bicalutamide compared with that in prostate cancer patients not treated with bicalutamide.

Study design

Retrospective cohort study with nested case-control analyses.

Subject population

Using data from the General Practice Research Database, all men aged 50–84 years with a first diagnosis of prostate cancer during 1999–2005 were identified (n = 5103) and compared with age- and calendar-date-matched controls (n = 20 000). All cases with a code of prostate cancer were manually reviewed to define final case status.

Two separate follow-up studies were performed from 1999–2006: the first assessed the occurrence of hospitalization due to acute myocardial infarction (AMI, n = 623) or death due to coronary heart disease (CHD, n = 189), and the second assessed the incidence of heart failure (HF, n = 323) and hospitalizations from acute decompensated HF (ADHF, n = 346). All cases with a code for any of the outcomes were manually reviewed. HF diagnosis was further validated through questionnaires to primary care physicians. Controls for the follow-up studies were randomly sampled within the prostate cancer cohort.

Exposure definition

All prescriptions issued by the primary care physician are recorded in the database and a coded drug dictionary (Multilex) is used to record prescribed medicines. Information on the type of androgen deprivation therapies (ADT) used between the start of follow-up and the index date was obtained from the computerized files. Specific information on antiandrogen therapy as a whole and the individual types of antiandrogen therapy used (bicalutamide, cyproterone and flutamide) was collected. For bicalutamide, data were collected on the two different doses that are available – 50 mg/day and 150 mg/day. Information was also collected for patients receiving luteinizing hormone-releasing hormone (LHRH) agonists and combination therapy.

Four subgroups for ADT exposure were defined: current use, recent use, past use and non-use. Current users were defined those whose most recent prescription ended 0–30 days before the index date; recent users were those whose most recent prescription ended 31 days to 1 year before the index date; past users were those patients whose most recent prescription ended more than 1 year before the index date; and non-users were those patients who had never had a prescription for any type of ADT.

Statistical methods

Poisson regression models were used to calculate incidence of each outcome among prostate cancer patients compare with that in the control cohort. Cox regression was performed to quantify the hazard ratio (HR) for the association between prostate cancer and each of the studied outcomes. HRs were adjusted for age, calendar year of start date and number of PCP visits in the year prior to prostate cancer diagnosis. Case–control analyses nested in the prostate cancer cohort were performed for the different types of treatment (odds ratios [ORs] and 95% confidence intervals [CIs] were estimated).

Summary of results

The overall incidence of prostate cancer in the UK in 1999–2005 was 3.71 per 1000 person-years. The incidence of prostate cancer increased markedly with age. At the time of diagnosis, 64.4% of patients were 70 years or older and the median age at diagnosis was 72 years.

The majority of patients (83.3%) received some form of prostate cancer treatment with 18.5% of patients receiving more than one treatment. Hormone therapy was the most commonly used treatment (used by 72.2% of patients), with 61.6% of patients who were prescribed hormone therapy receiving an LHRH agonist, 53.6% using antiandrogens and 5.9% taking oestrogens. Of the LHRH agonists, goserelin was prescribed to 53.1% of patients in the prostate cancer cohort, compared with 13.8% receiving leuprorelin. The most commonly used antiandrogen was bicalutamide, with 34.0% of patients receiving this treatment at any time during the study. Cyproterone was used by 23.5% and flutamide by 5.1% of men with prostate cancer.

Men with prostate cancer tended to have a slightly higher risk of hospitalization from AMI (HR: 1.14; 95% CI: 0.95–1.38), incident HF (HR: 1.24; 95% CI: 0.96–1.60) and hospitalization from ADHF (HR: 1.10; 95% CI: 0.85–1.41) than men without a diagnosis of prostate cancer, but these risks did not reach statistical significance. Men with prostate cancer had a lower risk of death from CHD (HR: 0.68; 95% CI: 0.46–1.01) than men without prostate cancer, but again this did not reach statistical significance.

The risk of CHD or HF in prostate cancer patients currently receiving various prostate cancer treatments is shown in Table 1.

There was no significant association between current use of antiandrogens, when assessed as group or considered individually, and the risk of hospitalization from AMI or CHD compared with non-use of any antiandrogens. Current use of LHRH agonists was associated with a significant increase in the overall risk of CHD compared with non-use of LHRH agonists. Prostate cancer patients currently taking a combination of LHRH agonists and antiandrogens had a significantly increased risk of hospitalization due to AMI and CHD compared with men not receiving either therapy.

Table 1 **Association between pharmacological therapy and the risk of cardiovascular outcomes in men with prostate cancer, compared with non-use of the respective therapy. Data show odds ratios and 95% confidence intervals**

Current treatment use	Hospitalization from AMI	CHD	Incident HF	Hospitalization from ADHF
Any antiandrogen	1.02 (0.55–1.90)	1.28 (0.75–2.20)	1.70 (0.85–3.40)	2.15 (1.08–4.29)
Bicalutamide 50 mg	1.24 (0.48–3.16)	1.64 (0.73–3.67)	1.54 (0.53–4.49)	3.28 (1.31–8.18)
Bicalutamide 150 mg	0.88 (0.34–2.27)	1.19 (0.53–2.64)	0.20 (0.03–1.52)	0.63 (0.18–2.23)
Any LHRH agonist	1.49 (0.93–2.40)	1.61 (1.04–2.51)	1.81 (0.93–3.52)	2.07 (1.06–4.05)
Antiandrogens and LHRH agonist	3.57 (1.44–8.86)	4.35 (1.94–9.75)	3.19 (1.10–9.27)	3.39 (1.07–10.7)

Current use of any antiandrogen and current individual use of bicalutamide 50 mg, was associated with a significantly increased risk of hospitalisation from ADHF but not incident HF, compared with non-use of any antiandrogens. The risk of hospitalization from ADHF was significantly associated with current use of LHRH agonists. Patients currently taking a combination of antiandrogens and LHRH agonists had a significantly increased risk of incident HF (OR: 3.19; 95% CI: 1.10–9.27) and hospitalization due to ADHF (OR: 3.39; 95% CI: 1.07–10.7) compared with men not taking either therapy.

Current bicalutamide use was not associated with a significantly increased risk of hospitalization from AMI, CHD or incident HF. As discussed above, the risk of hospitalization from ADHF was significantly associated with current use of bicalutamide 50 mg/day, but this was only true in patients receiving bicalutamide in conjunction with orchidectomy. No cases of hospitalization from ADHF were identified in patients taking bicalutamide 50 mg/day or 150 mg/day as monotherapy.